Remarks/Arguments:

In the Office Action, claims 1 and 16 were objected to for certain informalities and claim 13 was provisionally rejected as being a substantial duplicate of claim 1. Claims 1 and 16 have been amended to correct the noted informalities and claim 13 has now been canceled. Each of these grounds for rejection have accordingly been obviated.

An amendment has also been made to correct typographical errors in two paragraphs of the specification. Each of the foregoing changes is fully supported by the remainder of the specification and does not introduce any new matter into the application.

Claims 1 – 5 and 7-16 stand rejected under 35 USC § 102(e) as being anticipated by Petrus. Applicants respectfully traverse this rejection with respect to amended claim 1 and claims dependent thereon for the reasons set forth below.

Claim 1 as amended recites and is limited to an oral dosage form, that is, a dosage form for oral administration, as specifically disclosed at page 7, lines 17 – 20 of the specification. Petrus, on the contrary, teaches a topical formulation which is administered for application to and absorption through the skin. Thus, Petrus teaches directly away from the use of an oral dosage form for the treatment of pain. Further, the efficacy of Petrus' composition is dependent on inclusion of a penetration enhancer, whereas applicants composition as claimed does not contemplate use of such a penetration enhancer. Finally, Petrus is silent as to the significance of the 4:1 ratio of glucosamine to ibuprofen. In the context of a topical application it is virtually impossible to determine if that is a sub-additive or super-additive ratio or combination. Even if one were to assume for purposes of argument that it were super-additive, it would nevertheless be irrelevant to oral dosage forms because the factors governing absorption and activity of an orally administered analgesic cannot reasonably be predicted from data relating to a topically administered analgesic.

The distinction between topical and oral routes is clearly made by Petrus at column 2, lines 1-5: "The use of topical analgesic compositions to treat...is an effort to overcome the side

effects of oral preparations...." This divergence from oral administration is further supported at column 3, lines 37 – 40: "This topical administration offers a significant advantage over oral administration of therapeutic agents by overcoming the difficulty of poor gastrointestinal absorption...." In view of these clear teachings away from the use of orally administered compositions one skilled in the art would not be motivated to even explore the possibility of therapeutically more effective oral analgesic compositions.

Further, although Petrus teaches a topical ratio of 4:1 based on glucosamine sulfate, it is not predictable that the same ratio would apply to or confer advantages if applied to the oral route. In fact one skilled in the art would predict a different ratio because of pharmacokinetic factors associated with the oral route (col. 3, above). That is, doses given by one route produce magnitudes of effects different from those that are obtained when administered by a different route because the route determines the required blood and biophase concentrations.

In addition, synergistic interaction cannot be predicated on administration of a particular ratio by a different route. Synergism is, of course, an extremely rare phenomenon that must be documented with appropriate experimental/statistical rigor. Current pharmaceutical understanding does not allow a way to foresee synergism or even simple additivity for drug combinations. Thus, statements such as " one of ordinary sill in the art would expect the analgesic (efficacy) to be enhanced over ibuprofen alone" and "reasonable expectation of success" cannot be justified and do not apply to this rare phenomenon unless the teaching is such that the synergistic efficacy is clearly documented by the reference in question and for the route of administration in question. This may be demonstrated by reference to the combination of morphine and clonidine. Given spinally, these are synergistic in certain ratios, but when the same drugs are given systemically the result is simple additivity (See Ossipov et. al., J Pharmacol Exp Ther 255:1107, 1990). This concept is well known and is common knowledge to those skilled in the art of formulation of pharmaceutical compositions.

For these reasons claims 1-5 and 7-16 as amended are not anticipated or obvious in view of Petrus. Withdrawal of this rejection is respectfully requested.

Claims 1-4, 6, 7, 12, and 13 stand rejected under 35 USC 102(e) as being anticipated by Giorgetti. This rejection is respectfully traversed for the reasons set forth below.

Claim 1 has been amended to exclude salts or complexes of glucosamine having a counterion which has analgesic activity of its own, as expressly taught at page 4, lines 27-29 of the specification. Giorgetti's disclosure is limited to a glucosamine salt or complex with ketopro fen. Accordingly, claim 1 as amended and all claims dependent thereon now expressly exclude the salts or complexes taught by Giorgetti.

In the Office Action, at page 4, first full paragraph, it is stated: "Because there is no reduction in the anti-inflammatory effect of the salt as compared to the ketoprofen free acid... it is reasonable to conclude that the analgesic effect is also undiminished." This statement assumes the analgesic and anti-inflammatory actions are equivalent. On the contrary, it is well known that the analgesic and anti-inflammatory doses of NSAIDs are different. Anti-inflammatory activity and analgesic activity are simply two different phenomena that must be distinguished; one simply cannot be used as a basis to reasonably predict the other. For example, it is well known that the analgesic and anti-inflammatory doses of NSAIDs are different. The PDR (57th ed., 2003, page 1902-1903) lists the analgesic dose for ibuprofen in adults as 400 mg every 4 to 6 h and lists the dose for arthritis as 1200-3200 mg daily. That this difference is somehow related to greater pain in arthritis is discounted as the PDR states in regard to analgesia "... doses ... greater than 400 mg were no more effective than the 400 mg dose." A Similar distinction is made in Goodman & Gilman's The Pharmacological Basis of Therapeutics (page 639 of the 9th ed.). Further, equating an analgesic effect with an anti-inflammatory effect is not acceptable to the FDA as noted in the publication: Approved Drug Products With Therapeutic Equivalence Evaluations, 20th ed, Cumulative Supplement 12, December 2000, Section 1.3, relating to Diclofenac Sodium Ophthalmic solution, in which registration for post-operative pain was refused where the only efficacy data provided was for post operative relief of surgical inflammation.

Accordingly, applicants submit that the lack of reduction in <u>anti-inflammatory effect</u> of glucosamine as a salt in Giorgetti's Table 1 is irrelevant and would not reasonably teach or suggest a corresponding lack of reduction in <u>analgesic activity</u> either for that same salt or for any other combination of an analgesic and glucosamine.

For these reasons claims 1-4, 6, 7, 12, and 13 as amended are not anticipated or obvious in view of Giorgetti. Withdrawal of this rejection is respectfully requested.

Claims 1-5, 7, and 13-15 stand rejected under 35 USC 102(b) as being anticipated by Paradies. Specifically, it was stated that example 2 of Paradies teaches a salt of ibuprofen and glucosamine, and that, "Because the salt of Paradies contains two ingredients known to be useful for relief of pain (glucosamine and ibuprofen) one ordinarily skilled in the art would expect analgesic efficacy to be enhanced over ibuprofen alone..." Applicants respectfully disagree and submit that this reference does not teach or suggest the invention as set forth in amended claim 1 or any claim dependent thereon.

With respect to glucosamine, the examiner appears to be in error. That is, Paradies' example 2 does not disclose glucosamine as alleged, but rather discloses N-methyl glucamine as one of the components of Paradies salt or complex of ibuprofen. Secondly, no support has been provided for the alleged efficacy of N-methyl glucamine as an analgesic. Thus the Office Action is in error in two respects, namely, Paradies does not disclose a glucosamine salt of ibuprofen, nor does it disclose that glucosamine is itself an analgesic.

To the contrary, with respect to the analgesic activity of glucosamine, applicants have clearly demonstrated that it has no analgesic activity of its own (See page 10, lines 17 – 21 of the specification, reporting the results of test utilizing glucosamine alone and concluding that glucosamine itself does not provide relief from pain in the tests employed in applicants' invention). It is of course possible that N-methyl glucamine does provide some analgesia, whereas glucosamine itself does not. However, regardless of whether the Paradies' glucamine is or is not useful for pain, it is clear Paradies discloses a complex between the ibuprofen and the N-methyl glucamine, precisely the type of complex or salt that is now expressly excluded from amended claim 1.

Further, with respect to the allegation that one skilled in the art would expect analgesic efficacy to be enhanced, applicants respectfully submit that analgesic efficacy of combinations of drugs is inherently unpredictable, a fact generally accepted by pharmacologists and amply

demonstrated by the present specification and examples. For example (1) the combination of glucosamine with aspirin gave approximately 20% of the analgesia of aspirin alone (page 14, lines 18-20 and figure 3); (2) acetaminophen did not exhibit super-additive analgesia in combination with glucosamine sulfate and in general appeared to exhibit sub-additive analgesia, but may exhibit additive analgesia at selected dosages and ratios (page 15, lines 2-5); and (3) when tramadol was combined with glucosamine, the analgesic efficacy was substantially reduced at the ratios tested (page 15, lines 6-8).

For the foregoing reasons 1-5, 7, and 13-15 are not anticipated by or obvious from the Paradies reference. Applicants respectfully request reconsideration and withdrawal of this ground for rejection.

Claims 1 and 6 also stand rejected under 35 USC 103(a) as obvious in view of the teaching of Petrus. This ground for rejection is respectfully traversed for the same reasons as those given above with respect to the rejection under 35 USC § 102(e), that is, that Petrus leads directly away from an oral dosage form as claimed in amended claim 1, and that its teaching is limited to a topical formulation which includes a penetration enhancer`s for the very purpose of providing a route of administration other than oral. The issue is whether Petrus suggests an oral dosage form as claimed, not whether or not it would be obvious to substitute ketoprofen for ibuprofen in Petrus' topical formulation. Since Petrus' entire teaching is away from an oral analgesic, Petrus cannot reasonably teach, suggest or motivate an oral dosage form. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 1, 2, 14, and 15 stand rejected under 35 USC §103(a) as unpatentable over Giorgetti, on the ground that it would have been obvious to administer the salts of Giorgetti to a human. As indicated above claims 1, 14 and 15 have all been amended to exclude salts or complexes of glucosamine in which the counterion is itself an analgesic. Accordingly applicants respectfully submit that the amended claims patentably distinguish over the teaching of Giorgetti. Reconsideration and withdrawal is respectfully requested.

In view of the foregoing amendments and remarks, it is believed that the claims presented above are allowable over the art of record. An early notice of allowance is respectfully requested.

Respectfully submitted,

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Motrin—Cont.

Phenylketonurics: MOTRIN Chewable Tablets 50 mg contain phenylalanine 3 mg per tablet, and the 100 mg tablets contain phenylalanine 6 mg per tablet.
Diabetics: MOTRIN Suspension and MOTRIN Oral Drops contain 0.3 g sucrose and 1.6 calories per mL, or 1.5 g sucrose and 8 calories per teaspoon, which should be taken into consideration when treating diabetic patients with this product.
Information for Patients—MOTRIN, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.
NSAIDs are often essential agents in the management of arthritis, pain and fever, but they also may be commonly employed for conditions which are less serious.
Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.
Patients on MOTRIN should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.
Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see WARNINGS).
Patients should also be instructed to seek medical emergency help in case of an occurrence of an anaphylactoid reaction (see WARNINGS).

LABORATORY TESTS

Hemoglobin Levels: In cross-study comparisons, in adults, with doses ranging from 1200 mg to 3200 mg daily for several weeks, a slight dose-response decrease in hemoglobin/hematocrit was noted. This has been observed with other nonsteroidal anit-inflammatory drugs; the mechanism is unknown. However, even with daily doses of 3200 mg, the total decrease in hemoglobin usually does not exceed 1 g/dL; if there are no signs of bleeding, it is probably not clinically important.
In two postmarketing clinical studies with ibuprofen, the incidence of a decreased hemoglobin level was greater than previously reported. Decrease in hemoglobin of 1 g/dL or more was observed in 17.1% of 193 patients on 1600 mg ibuprofen daily (osteoarthritis), and 22.8% of 189 patients taking 2400mg of ibuprofen daily (rheumatoid arthritis). Positive stool occult blood tests and elevated serum creatinine levels were also observed in these studies.

DRUG INTERACTIONS

Coumarin-type anticoagulants: Several short-term controlled studies failed to show that iburprofen significantly affected prothrombin times or a variety of other clotting factors administered to individuals on coumarin-type anticoagulants. Because bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants, the physician should be cautious when administering MOTRIN to patients on anticoagulants.
Aspirin: Animal studies show that aspirin given with NSAIDs, including ibuprofen, yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-aspirin drug. Single-dose bioavailability studies in normal volunteers have failed to show an effect of aspirin on ibuprofen blood levels. Correlative clinical studies have not been done.
Methotrexate: Ibuprofen, as well as other NSAIDs, has been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used, therefore, if MOTRIN is administered concomitantly with methotrexate.
H-2 Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.
ACE-inhibitors: Reports suggest that NSAIDs, including ibuprofen, may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking MOTRIN concomitantly with ACE-inhibitors.
Furosemide: Clinical studies, as well as random observations, have shown that ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with MOTRIN, the patient should be observed closely for signs of renal failure (see PRECAUTIONS, Renal Effects), as well as to assure diuretic efficacy.
Lithium: Ibuprofen produced an elevation of plasma lithium levels and a reduction in renal lithium clearance in a study of eleven normal volunteers. The mean minimum lithium concentration increased 15% and the renal clearance of lithium was decreased by 19% during this period of concomitant drug administration. This effect has been attributed to inhibition of renal prostaglandin synthesis by ibuprofen. Thus, when MOTRIN and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity. (Read circulars for lithium preparation before use of such concurrent therapy.)
Teratogenic Effects—Pregnancy Category B: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. Administration of MOTRIN is not recommended during pregnancy.
Labor and Delivery: As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of MOTRIN is not recommended during labor and delivery.
Nursing Mothers: In limited studies, an assay capable of detecting 1 µg/mL did not demonstrate ibuprofen in the milk of lactating mothers. Because of the limited nature of these studies, however, and the possible adverse effects of prostaglandin inhibiting drugs on neonates, MOTRIN is not recommended for use in nursing mothers.
Pediatric Use: Safety and efficacy of MOTRIN in children below the age of 6 months has not been established (see CLINICAL PHARMACOLOGY-Clinical Studies). There is no evidence of age-dependent kinetics in patients 2 to 11 years old (see CLINICAL PHARMACOLOGY-Pharmacokinetics). Dosing of MOTRIN in children 6 months or older should be guided by their body weight (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.
In controlled studies in adults, when ibuprofen was compared to aspirin and indomethacin in equally effective doses, the overall incidence of gastrointestinal complaints was about half that seen in either the aspirin- or indomethacin-treated patients.
Adverse reactions observed during controlled clinical trials in adults at an incidence greater than 1% are listed in the chart. Those reactions listed under the heading "Incidence Greater than 1% (but less than 3%) Probable Causal Relationship," encompass observations in approximately 3,000 patients. More than 500 of these patients were treated for periods of at least 54 weeks.
Still other reactions, occurring less frequently than 1 in 100, were reported in controlled clinical trials and from marketing experience. These reactions have been divided into two categories: "Incidence less than 1%—Probable Causal Relationships," lists reactions with Ibuprofen therapy for which the probability of a causal relationship exists; this category was completed over time with postmarketing serious adverse reactions. "Incidence less than 1% —Causal Relationship Unknown," lists reactions with ibuprofen therapy for which a causal relationship has not been established, but are presented as alerting information for physicians.

INCIDENCE OF 1% OR GREATER

Probable Causal Relationship
*Incidence between 3 and 9%=ADR marked with**
Incidence between 1 and <3%=unmarked ADR
Cardiovascular system: Edema, fluid retention (generally responds promptly to drug discontinuation) (See PRECAUTIONS).
Digestive system: Nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence).
Nervous system: Dizziness*, headache, nervousness.
Skin and appendages: Rash* (including maculopapular type), pruritus
Specal senses: Tinnitus.

INCIDENCE LESS THAN 1%

Probable Causal Relationship: The following adverse reactions were reported in clincial trials at an incidence of less than 1%, or were reported from postmarketing or foreign experience. The probability exists between the drug and these adverse reactions.
Body as a whole: Anaphylaxis and anaphylactoid reactions (see WARNINGS).
Cardiovascular system: Cerebrovascular accident, hypotension, congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations.
Digestive system: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, pancreatitis, melena, gastritis, duodenitis, esophagitis, hematemesis, hepatorenal syndrome, liver necrosis, liver failure, hepatitis, jaundice, abnormal liver tests.
Hematologic system: Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decrease in hemoglobin and hematocrit (see PRECAUTIONS), pancytopenia.
Nervous system: Depression, insomia, confusion, emotional liability, somnolence, convulsions, aseptic meningitis with fever and coma (see PRECAUTIONS).
Respiratory: Bronchospasm, dyspnea, apnea.
Skin and appendages: Vesiculobullous e… ria, erythema multiforme, Stevens-Johnson… pecia, exfoliative dermatitis, Lyell's syndro… mal necrolysis), photosensitivity reactions.
Special senses: Hearing loss, amblyopia… diminished vision, scotomata and/or change… (see PRECAUTIONS—Other Precautions).
Urogenital system: Acute renal failure in… pre-existing significantly impaired renal fun… CAUTIONS), renal papillary necrosis, tubul… merulitis, decreased creatinine clearance… mia, cystitis, hematuria.
Miscellaneous: Dry eyes and mouth, gingi… tis.

INCIDENCE LESS THAN 1%

Causal Relationship Unknown: The follow… actions occurred at an incidence of less than… trials, or were suggested by marketing experi… cumstances where a causal relationship … nitely established. They are listed as alerti… for the physician.
Allergic: Serum sickness, lupus erythemat… Henoch-Schönlein vasculitis, angioedema…
Cardivascular system: Arrhythmias (sinus … nus bradycardia).
Hematologic system: Bleeding episodes … menorrhagia).
Metabolic/endocrine: Gynecomastia, hypo… tion, acidosis.
Nervous system: Paresthesias, hallucinati… normalities, pseudo-tumor cerebri.
Special senses: Conjunctivitis, diplopia, … cataracts.

OVERDOSAGE

The *toxicity of ibuprofen overdose* is depen… amount of drug ingested and the time elapse… tion, though individual response may vary, … necessary to evaluate each case individually. … common, serious toxicity and death have be… the medical literature with ibuprofen overdos… frequently reported symptoms of ibuprofen … abdominal pain, nausea, vomiting, lethargy, … ness. Other central nervous system symptoms … ache, tinnitus, CNS depression and seizures … idosis, coma, acute renal failure and apne… very young children) may rarely occur. Card… icity, including hypotension, bradycardia, … atrial fibrillation, also have been reported.
The *treatment of acute ibuprofen overdose* is … portive. Management hypotension acidosis and … tinal bleeding may be necessary. In cases of a… the stomach should be emptied through ipeca… esis or lavage. Emesis is most effective if initia… minutes of ingestion. Orally administered … coal may help in reducing the absorption and … of ibuprofen.
In children, the estimated amount of ibuprofen … body weight may be helpful to predict the po… velopment of toxicity although each case must … Ingestion of less than 100 mg/kg is unlikely … icity. Children ingesting 100 to 200 mg/kg may … with induced emesis and a minimal observation … hours. Children ingesting 200 to 400 mg/kg … should have immediate gastric emptying and … hours observation in a health care facility. Ch… ing greater than 400 mg/kg require immediate … ferral, careful observation and appropriate su… apy. Ipecac-induced emesis is not recommen… doses greater than 400 mg/kg because of … convulsions and the potential for aspiration … tents.
In adult patients the history of the dose repor… does not appear to be predictive of toxicity. Th… ferral and follow-up must be judged by the cir… the time of the overdose ingestion. Sympto… should be admitted to a health care facility …

DOSAGE AND ADMINISTRATION

CHILDREN

Fever reduction: For reduction of fever … months to 12 years of age, the dosage should … the basis of the initial temperature level tak… PHARMACOLOGY). The recommended dose … the baseline temperature is less than 102.5°F, … the baseline temperature is 102.5°F or great… tion of fever reduction is generally 6 to 8 hou… mended maximum daily dose is 40 mg/kg.
Analgesia: For relief of mild to moderate pai… 6 months to 12 years of age, the recommen… 10 mg/kg, every 6 to 8 hours. The recommen… daily dose is 40 mg/kg. Doses should be give… disturb the child's sleep pattern. Taking fluids … MOTRIN Chewable Tablets may help to pro… of the drug (see CLINICAL PHARMACOLO… cokinetics, and "Individualization of Dosage… tion).
Juvenile Arthritis: The recommended dose … kg/day divided into three to four doses (see … tion of Dosage). Patients with milder disease … quately treated with 20 mg/kg/day.

ADULTS

Analgesia: 400 mg every 4 to 6 hours as nee… relief of mild to moderate pain in adults. In … algesic clincial trials, doses of MOTRIN … 400 mg were no more effective than the 400…

...bullous eruption...
...as-Johnson syndrome...
...'s syndrome (...
...reactions...
...mblyopia (blur...
...or changes in co...
...cautions)...
...l failure in pati...
...l renal function...
...osis, tubular ne...
...learance, polyu...
...uth, gingival ul...
...The following ad...
...f less than 1% ...
...ing experience ...
...onship could not...
...l as alerting in...
...rythematosus s...
...edema...
...as (sinus tachyc...
...pisodes (e.g., ...
...tia, hypoglycem...
...llucinations, dr...
...iplopia, optic ...
...is dependent upo...
...ne elapsed since ...
...y vary, which ma...
...ividually. Althou...
...have been report...
...overdosage. The...
...profen overdose ...
...lethargy and dr...
...ymptoms include ...
...eizures, Metabo...
...d apnea (primar...
...ur. Cardiovascul...
...rdia, tachycard...
...orted...
...dose is primarily ...
...dosis and gastro...
...ses of acute ov...
...h ipecac-induced ...
...if initiated with...
...tered activated ...
...tion and reabs...
...buprofen ingest...
...the potential for ...
...se must be eva...
...likely to produce ...
.../kg may be ma...
...ervation time of ...
...mg/kg of ibupro...
...ng and at least ...
...lity. Children ma...
...mediate medical ...
...iate supportive ...
...ommended in ...
...se of the risk ...
...ation of gastric ...
...reportedly ingest...
...ity. The need for ...
...he circumstances ...
...ymptomatic after...
...lity for observa...
...ver in children...
...ould be adjusted ...
...el (see CLINICAL ...
...dose is 5 mg/kg ...
...5°F, or 10 mg/kg ...
...greater. The ...
...hours. The ...
...e pain in ch...
...mended dos...
...nended ma...
...given so as ...
...nids after ch...
...OLOGY—P...
...sage" in ...
...se is 30 to ...
...ee Individ...
...ase may b...
...necessary. ...
...In controlled ...
...N greater ...
...0 mg dos...

...morrhea: For the treatment of pr... dys- ...beginning with the earliest onset of ... pain, ...ould be given in a dose of 400 mg every 4 hours, ... for the relief of pain.

...arthritis and osteoarthritis, including flare-ups ...assess: Suggested dosage: 1200-3200 mg daily ...d or 400 mg, 600 mg or 800 mg t.i.d. or q.i.d.). ...atients may show a better response to 3200 mg ...mpared with 2400 mg, although in well-con- ...ical trials patients on 3200 mg did not show a ... response in terms of efficacy. Therefore, when ...atients with 3200 mg/day, the physician should ...cient increased clincial benefits to offset poten- ...d risk.

...tion of Dosage The dose of MOTRIN should be ... each patient, and may be lowered or raised from ...d doses depending on the severity of symptoms ...se of initiating drug therapy or as the patient ... fails to respond.

...study showed that, after the initial dose of MOT- ...quent doses may be lowered and still provide ad- ...r control.

...ion when low fever would require the MOTRIN ...se in a child with pain, the dose that will effec- ... the predominant symptom should be chosen.

... conditions, a therapeutic response to MOTRIN ...s sometimes seen in a few days to a week, but most ...erved by two weeks. After a satisfactory response ...achieved, the patient's dose should be reviewed ...ted as required.

...ts with juvenile arthritis, doses above 50 mg/kg/ ...not recommended because they have not been stud- ... doses exceeding the upper recommended dose of ...day may increase the risk of causing serious ad- ...nts. The therapeutic response may require from a ... to several weeks to be achieved. Once a clincial ...obtained, the dosage should be lowered to the small- ... of MOTRIN needed to maintain adequate control of ...

...l patients with rheumatoid arthritis seem to re- ...uire doses than do patients with osteoarthritis. The ... dose of MOTRIN that yields acceptable control ... employed.

...SUPPLIED

... (ibuprofen) Suspension 100 mg/5 mL
...-colored, berry-flavored suspension
... of 120 mL—NDC 0045-0448-04
... of 480 mL—NDC 0045-0448-16
...well before using. Store at controlled room tempera- ...15° to 30°C (59° to 86°F)]

... (ibuprofen) Oral Drops, 40mg/mL
...ed for pediatric use only)
...ored, berry flavored suspension
... of 15 ml—NDC 0045-0446-15
...well before using. Store at controlled room tempera- ...15° to 30°C (59° to 86°F)].

... (ibuprofen) Chewable Tablets, 50 mg
... orange-colored, citrus-tasting, scored tablet, de- ...MOTRIN 50"
... of 100 Chewable Tablets—NDC 0045-0361-10
... controlled room temperature [15° to 30°C (59° to ...

... (ibuprofen) Chewable Tablets, 100 mg
... orange-colored, citrus-tasting, scored tablet, de- ...MOTRIN 100"
... of 100 Chewable Tablets—NDC 0045-0431-10
... controlled room temperature [15° to 30°C (59° to ...

... (ibuprofen) Caplets, 100 mg
...-colored, scored capsule-shaped tablet, imprinted "M ...
... of 100 Caplets—NDC 0045-0445-10
... controlled room temperature [15° to 30°C (59° to ...

... Federal Law prohibits dispensing without pre- ...

... CONSUMER PRODUCTS CO.
...ION OF McNEIL-PPC, INC.
... WASHINGTON, PA 19034-USA
...BER 1994
...own in Product Identification Guide, page 321

...IN® MIGRAINE PAIN CAPLETS OTC

...IPTION

...Motrin® Migraine Pain Caplet contains ibuprofen ...

...ain of migraine headache

...TIONS

...	• take 1 or 2 caplets with a glass of water • the smallest effective dose should be used • if symptoms persist or worsen, ask your doctor
...	• do not take more than 2 caplets in 24 hours for pain of migraine unless directed by a doctor
under 18 years of age:	• ask a doctor

WARNINGS

Allergy alert: ibuprofen may cause a severe allergic reaction which may include:
- hives • facial swelling
- asthma (wheezing) • shock

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take ibuprofen or other pain relievers/fever reducers. Ibuprofen may cause stomach bleeding.

Do not use if you have ever had an allergic reaction to any other pain relievers/fever reducer

Ask a doctor before use if you have
- never had migraines diagnosed by a health professional
- a headache that is different from your usual migraines
- the worst headache of your life
- fever and stiff neck
- headaches beginning after or caused by head injury, exertion, coughing or bending
- experienced your first headache after the age of 50
- daily headaches
- a migraine headache so severe as to require bed rest
- problems or serious side effects from taking pain relievers or fever reducers
- stomach pain
- vomiting with your migraine headache

Ask a doctor or pharmacist before use if you are
- under a doctor's care for any serious condition
- taking any other drug
- taking any other product that contains ibuprofen, or any other pain reliever/fever reducer

Stop use and ask a doctor if
- an allergic reaction occurs. Seek medical help right away.
- migraine headache pain is not relieved or gets worse after first dose
- stomach pain or upset gets worse or lasts
- new or unexpected symptoms occur

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Other Information:
- do not use if neck wrap or foil inner seal imprinted **"Safety Seal"** is broken or missing
- store at 20–25°C (68–77°F)

Professional Information:
OVERDOSAGE Information

For overdosage information, please refer to page 1904.

Inactive Ingredients: carnauba wax, corn starch, hypromellose, iron oxide, polydextrose, polyethylene glycol, propylene glycol, silicon dioxide, stearic acid, titanium dioxide

HOW SUPPLIED

Caplets (white printed "Motrin M" in black) in tamper evident packaging of 24, 50, and 100

Shown in Product Identification Guide, page 321

MOTRIN® Sinus/Headache Caplets OTC

DESCRIPTION

Each MOTRIN® Sinus/Headache Caplet contains ibuprofen 200 mg and pseudoephedrine HCl 30 mg.

USES

temporarily relieves these symptoms associated with the common cold, sinusitis, and flu:
- headache • nasal congestion
- fever • minor body aches and pains

DIRECTIONS

Adults and children 12 years and older	• take 1 caplet every 4 to 6 hours while symptoms persist • If symptoms do not respond to 1 caplet, 2 caplets may be used. • do not use more than 6 caplets in any 24-hour period unless directed by a doctor • the smallest effective dose should be used
Children under 12 years of age	Consult a doctor

WARNINGS

Allergy alert: Ibuprofen may cause a severe allergic reaction which may include:
- hives • facial swelling
- asthma (wheezing) • shock

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take ibuprofen or other pain relievers/fever reducers. Ibuprofen may cause stomach bleeding.

Do not use if you
- have ever had an allergic reaction to any other pain reliever/fever reducer
- are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson's disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

Ask a doctor before use if you have
- heart disease • high blood pressure
- thyroid disease • diabetes
- trouble urinating due to an enlarged prostate gland
- had serious side effects from taking any pain reliever/fever reducers.

Ask a doctor or pharmacist before use if you are
- taking any other product that contains ibuprofen or pseudoephedrine.
- taking any other pain reliever/fever reducer or nasal decongestant
- under a doctor's care for any continuing medical condition
- taking other drugs on a regular basis

When using this product
- **do not use more than directed**
- give with food or milk if stomach upset occurs

Stop use and ask a doctor if
- an allergic reaction occurs. Seek medical help right away
- you get nervous, dizzy, or sleepless
- nasal congestion lasts for more than 7 days
- symptoms continue or get worse
- new or unexpected symptoms occur
- stomach pain occurs with use of this product or even if mild symptoms persist
- fever lasts for more than 3 days

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use this product during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Other Information:
- **do not use if blister unit is broken or open**
- Store at 20–25°C (68–77°F).
- avoid excessive heat above 40°C (104°F)
- read all warnings and directions before use. Keep carton.

Professional Information:
OVERDOSAGE INFORMATION

For overdosage information, please refer to page 1904.

INACTIVE INGREDIENTS

Caplets: carnauba wax, cellulose, corn starch, FD&C Red #40, hypromellose, silicon dioxide, sodium lauryl sulfate, sodium starch glycolate, stearic acid, titanium dioxide, triacetin.

HOW SUPPLIED

Caplets: (white, printed "Motrin Sinus/Headache" in red) in blister packs of 20 and 40.

Shown in Product Identification Guide, page 321

Infants' MOTRIN® ibuprofen Concentrated Drops OTC

Children's MOTRIN® ibuprofen Oral Suspension and Chewable Tablets

Junior Strength MOTRIN® ibuprofen Caplets and Chewable Tablets

Product information for all dosages of Children's MOTRIN have been combined under this heading

DESCRIPTION

Infants' MOTRIN® Concentrated Drops are available in an alcohol-free, berry-flavored suspension and a non-staining, dye-free, berry-flavored suspension. Each 1.25 mL contains ibuprofen 50 mg. *Children's MOTRIN® Oral Suspension* is available as an alcohol-free, berry, dye-free berry, bubblegum or grape-flavored suspension. Each 5 mL (teaspoon) of *Children's MOTRIN® Oral Suspension* contains ibuprofen 100 mg. Each *Children's MOTRIN® Chewable Tablet* contains 50 mg of ibuprofen and is available as orange or grape-flavored chewable tablets. *Junior Strength MOTRIN®*

Continued on next page

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An Isobolographic Analysis of the Antinociceptive Effect of Systemically and Intrathecally Administered Combinations of Clonidine and Opiates

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ABSTRACT

The antinociceptive interaction of opiate analgesics with clonidine was examined with the tail-flick and 55°C hot plate tests. Male Sprague-Dawley rats received fixed ratios of clonidine to fentanyl, meperidine or morphine by i.v. and intrathecal injection. Data are expressed as percentage of maximal possible effect and the dose producing 50 percentage of maximal possible effect for each drug or drug combination is used to index potency. The rank order of potency in both tests after i.v. administration is fentanyl ≫ clonidine > meperidine ≥ morphine and after intrathecal administration it is morphine > fentanyl ≫ clonidine ≫ meperidine. Isobolographic analysis shows that the effect of clonidine combined with an opiate is additive after i.v. administration; the exception is that morphine and clonidine are synergistic in the hot plate test. The intrathecal combinations of clonidine with morphine or meperidine produces a supra-additive antinociceptive effect in the tail-flick test but not in the hot plate test. Fentanyl does so in both tests. These data confirm a positive interaction between clonidine and opiates in producing antinociception. This interaction may be additive or synergistic, depending on route of administration and the nociceptive test used. The timing of injections and pharmacokinetic factors may also influence the results. Moreover, these results suggest that the interaction between the opiate and *alpha*-2 adrenergic receptors occurs within the spinal cord.

Opioid analgesic agents may modulate responses to nociceptive stimuli by activating descending inhibitory pathways and also by acting directly on the spinal cord. The antinociceptive effect of systemically, but not i.t., administered morphine is diminished by spinal transection in rats, indicating both a supraspinal and direct spinal effect of opiates (Advokat and Burton, 1987). The activation of opiate receptors reduces the activity of nocisponsive neurons in the dorsal horn of the spinal cord, either directly or by reducing the outflow of neurotransmitters activating these neurons (Yaksh, 1985; Yaksh and Noueihed, 1985). A supraspinal site of action of opiates involves the activation of descending monoaminergic projections that reduce the responses of nocifensive neurons to noxious stimuli in the spinal cord (Hammond and Yaksh, 1984; Yaksh, 1979, 1985).

There is a significant noradrenergic involvement in the expression of opiate-induced antinociception (Camarata and Yaksh, 1985) which is expressed by spinal *alpha*-2 adrenoceptors (Howe *et al.*, 1983; Hylden and Wilcox, 1983). The spinal administration of noradrenergic agonists augmented morphine and stimulation produced antinociception whereas the administration of an antagonist attenuated the effect of such treatments (Hylden and Wilcox, 1983; Reddy *et al.*, 1980; Sagen and Proudfit, 1984; Wigdor and Wilcox, 1987). A major role in opiate and stimulation produced antinociception results from the activation of spinal *alpha*-2 adrenergic receptors by noradrenergic neurons (Yaksh, 1985). These receptors regulate the responses of primary afferent neurons to nociceptive stimuli.

The iontophoretic administration of clonidine, a prototypic *alpha*-2 agonist, to neurons sensitive to nociceptive stimuli has reduced the firing rates of these neurons in response to a nociceptive stimulus (Murata *et al.*, 1989). Intrathecal administration of clonidine produces antinociception in mice (Ossipov *et al.*, 1989), rats (Milne *et al.*, 1985), primates (Yassh and Reddy, 1981) and sheep (Eisenach *et al.* 1987), and is used clinically to alleviate cancer (Coombs *et al.*, 1986) and postoperative (Boico *et al.*, 1988) pain. Fielding *et al.* (1981) established a positive interaction between systemically administered clonidine and morphine. The effect of morphine administered systemically (Drasner and Fields, 1988) or spinally (Hylden and Wilcox, 1983; Ossipov *et al.*, 1984; Wilcox *et al.*, 1987) is increased by i.t. clonidine. The observations that spinal transection of mice reduced the antinociceptive potency of morphine but not of clonidine (Spaulding *et al.*, 1979) and the fact that the central administration of *alpha*-2 adrenergic agonists in the locus ceruleus (Ossipov *et al.*, 1984), periaqueductal gray

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ABBREVIATIONS: i.t., intrathecal; TF, tail flick; HP, hot plate; %MPE, percentage of maximal possible effect; A_{50}, 50% analgesic dose.

or lateral reticular nucleus (Ossipov and Gebhart, 1983, 1986) failed to produce any antinociception suggest that *alpha*-2 receptor-mediated antinociception is not a supraspinal phenomenon.

The studies cited above along with a study by Wigdor and Wilcox (1987) show that spinal *alpha*-2 adrenergic receptors contribute significantly to the expression of opiate-mediated antinociception. *Alpha*-2 adrenergic receptors may act independently of the opiate system because clonidine-induced antinociception is not fully reversed by naloxone, still occurs in the presence of tolerance to the opiates and does not show complete cross-tolerance to morphine (Ossipov *et al.*, 1989; Solomon and Gebhart, 1988; Stevens *et al.*, 1988). A number of studies have shown that the coadministration of an opiate, typically morphine, with clonidine augments the effect of the opiate. The systemic administration of morphine increased the potency of clonidine applied i.t. in rats (Drasner and Fields, 1988). Systemic administration of clonidine or guanfacine produced dose-dependent elevations in the antinociceptive effect of etorphine administered in the periaqueductal gray of the cat, and this effect was attenuated by yohimbine (Ossipov *et al.*, 1984). Others have shown that the administration of a single dose of clonidine produced a shift to the left of the dose-response curve for morphine in the rat TF test (Wilcox *et al.*, 1987). These studies are interpreted as evidence that clonidine potentiates the antinociceptive effect of morphine.

The nature of the positive interaction (*i.e.*, additive or supraadditive) between opiates and *alpha*-2 agonists with regard to enhancement of antinociception has not been studied rigorously; thus, we are uncertain whether this interaction is truly synergistic or additive, or if synergy depends on the dose ratio used. Moreover, most of the data regarding interactions between opiates and *alpha*-2 agonists involved morphine; little has been reported regarding the interaction of structurally different opiates with clonidine. The experiments described here were undertaken to examine the antinociceptive interaction of fentanyl and meperidine (phenylpiperidines) and morphine (a morphinan) with clonidine, and to analyze the nature of this interaction by isobolographic analysis.

Methods

Analgesiometric Tests

TF test. The TF test of D'Amour and Smith (1947) was performed by placing the tail of male Sprague-Dawley rats (175–225 g) under a focused radiant heat source and over a photocell. The light was activated with a timer and, when the animal flicked its tail aside, the photocell was uncovered, stopping the timer. TF latencies were recorded (to 1/10th of a second) twice before and at several time periods after injection. A cutoff TF latency of either 10 sec in intact rats or 7 sec in catheterized rats was used to prevent tissue damage.

HP test. HP latencies were determined by placing each rat on an HP kept at 55 ± 0.5°C and observing the occurrence of one of the following nociceptive responses: 1) licking of the paws; 2) stomping of the hind paws; or 3) jumping out of the enclosure.

A timer was started when the animal was placed on the HP surface and stopped when the first nociceptive response was observed. The HP latencies were determined twice before and at several time periods after injection. A cutoff HP latency of 30 sec was used to prevent tissue damage.

Injection Protocols

Intravenous injections. Clonidine, fentanyl, meperidine and morphine were dissolved in 0.9% w/v saline and injected in a volume of 1 ml/kg into the lateral tail vein. The TF and HP latencies were determined at several time intervals after injection to establish the time of peak effect. Dose-response curves were determined at the time of peak effect. Injections were timed so that the peak effect of clonidine and the opiate coincided. Doses were administered to maintain fixed ratios of clonidine to fentanyl, meperidine and morphine. Ratios of clonidine/fentanyl were 2:1, 1:1, 1:2, 1:10, 10:1, 30:1 and 100:1. Those for clonidine/meperidine and clonidine/morphine were 1:3, 1:10, 1:30 and 1:100.

Intrathecal injections. Rats were prepared for i.t. drug injection according to the method described originally by Yaksh and Rudy (1976). A PE-10 catheter was inserted, under anesthesia with isoflurane, through the atlantooccipital membrane to the level of the lumbar enlargement of the spinal cord. The catheter was exteriorized at the back of the head, plugged and the wound was closed. The rats were allowed to recover for 1 week before undergoing any testing. Drugs were dissolved in 0.9% w/v saline and administered in a volume of 5 μl and the catheter was flushed with 10 μl of saline. The drugs were coadministered in the same solution to minimize the addition of fluid to the cerebrospinal fluid. The HP and TF latencies were measured at several time periods after injection and dose-response curves were constructed from data gathered at the time of peak effect.

Data Analysis

The data obtained were converted to %MPE by the equation:

$$\%\ \text{MPE} = 100 \times \frac{\text{Test latency} - \text{control latency}}{\text{cutoff} - \text{control latency}}$$

The log dose was plotted *vs.* %MPE and regression analysis of the log dose-response curve was used to calculate the A_{50} and its 95% CL.

The interaction between clonidine and the opiates was examined by isobolographic analysis. All doses are shown as the total (*i.e.*, opiate plus clonidine) drug administered. The opiate A_{50} is plotted on the ordinate and the clonidine A_{50} on the abscissa. A theoretical line of additive interaction is drawn by connecting the A_{50} for the opiate with that of clonidine. For each clonidine-opiate combination, an A_{50} along with confidence intervals is calculated for each mixture. For each combination there also exists a theoretical additive A_{50} that would be expected if the drug interaction was additive. This value may be obtained from the calculation: $A_{50add} = A_{50opiate}(p_1 + Rp_1)$ where R is the potency ratio of the opiate alone to clonidine alone, p_1 is the proportion of opiate administered in the total dose and p_2 is that of clonidine. Variances and CL for the theoretical A_{50} may also be calculated from the variances of each component administered alone (Tallarida *et al.*, 1989). This value is compared to the actual A_{50} obtained for the mixture of drugs using a t test. If the actual A_{50} is not different from the theoretical additive A_{50}, then the effect of the drug combination is additive; otherwise, a significant ($P \leq .05$) potency ratio in which the mixture A_{50} is less than the theoretical additive A_{50} indicates that the effect of the mixture is synergistic. A full description of the derivation and application of this method of analysis of drug interactions is provided by Tallarida *et al.* (1989).

Results

Dose-related antinociception of clonidine and opiates i.v. All agents tested produced dose-dependent antinociception in both tests. The A_{50} doses for clonidine, fentanyl, meperidine and morphine were 0.11, 0.0031, 1.66 and 1.77 mg/kg, respectively, in the rat TF test and 0.26, 0.0072, 3.2 and 4.4 mg/kg, respectively, in the rat HP test. The rank-order potency in both tests was fentanyl >> clonidine >> meperidine ≥ morphine. Moreover, the dose-response curves within the TF (fig. 1A) and the HP (fig. 1B) tests did not deviate significantly from parallelism, thus suggesting a common final mechanism of action for antinociceptive activity. The A_{50} doses and the confidence intervals for both tests are summarized in table 1.

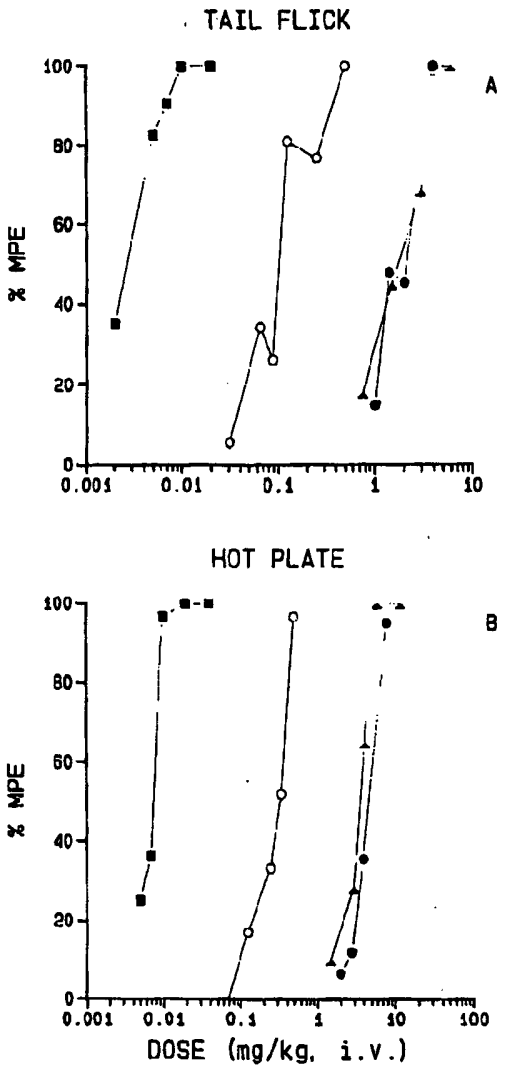

Fig. 1. Dose-response curves for the TF (A) and HP (B) tests. Morphine (●), meperidine (▲), fentanyl (■) and clonidine (○) were administered to rats by i.v. injection and responses were converted to %MPE for each test. $n = 6$/dose.

Interaction of clonidine and opiates i.v. Clonidine produced a peak effect at 15 min after injection, fentanyl at 1 min and meperidine and morphine at 5 min after injection. Thus, all testing of the interaction between opiates and clonidine was done at 15 min after clonidine injection and the timing of injections was arranged so that the peak effect of the opiate and clonidine coincided. The total A_{50} values for each clonidine-opiate combination are shown in table 1. For each combination the dose-response curves were parallel to the dose-response curve for morphine and for clonidine within each test.

Isobolographic analysis of i.v. clonidine-opiate interactions. The data for the combinations of opiates and clonidine are represented as isobolograms in figure 2. In all the graphs presented, the doses of clonidine are shown on the abscissa and those of opiate are on the ordinate. Thus, in the first example, the A_{50} for clonidine (0.11 mg/kg) in the TF test is shown at point (0.11,0) and that for morphine (1.77 mg/kg) is plotted at (0,1.77); these points are connected by a solid theoretical line of additivity. For each morphine-clonidine combination, the

TABLE 1

Changes in potency elicited by clonidine i.v.

Dose-response curves were constructed for fixed ratios of clonidine and fentanyl, morphine and meperidine in the rat TF and HP tests. The drug ratios are identified as clonidine to opiate. The A_{50} values are calculated from the log dose-response curve by linear regression. The clonidine and opiate components of the A_{50} for each combination can be calculated from the ratio. For a clonidine to morphine ratio of 1:10 in the TF test, the clonidine component is 0.059 mg/kg (1/11 of 0.65) and the morphine component is 0.59 (10/11 of 0.65). Thus, although morphine appears to be potentiated, the dose of clonidine used is close to the equiefficacious dose of clonidine given alone. Each dose was administered by i.v. injection and the animals were tested at the time of peak effect. $n = 6$ animals per dose.

	A_{50} mg/kg (95% CL)	
	Rat TF Test	Rat HP Test
Clonidine/fentanyl		
No clonidine	0.0031 (0.0017–0.0056)	0.0072 (0.0029–0.018)
1:10	0.0029 (0.0013–0.0064)	0.0066 (0.0049–0.0107)
1:2	0.0061 (0.0021–0.018)	0.018 (0.010–0.031)
1:1	0.0108 (0.0092–0.126)	0.0174 (0.0092–0.034)
2:1	0.0123 (0.0069–0.0222)	0.0243 (0.0210–0.0285)
10:1	0.0201 (0.0165–0.0275)	0.0385 (0.0275–0.0550)
30:1	0.0527 (0.0372–0.0775)	0.0868 (0.0713–0.105)
100:1	0.101 (0.0869–0.192)	0.202 (0.162–0.252)
Clonidine/morphine		
No clonidine	1.77 (1.1–2.8)	4.4 (3.0–6.4)
1:3	0.267 (0.15–0.49)	0.53 (0.29–0.94)
1:10	0.65 (0.45–0.94)	1.00 (0.91–1.09)*
1:30	0.64 (0.090–4.5)	1.6 (1.01–2.5)*
1:100	0.95 (0.47–1.9)	2.6 (1.6–4.4)
Clonidine/meperidine		
No clonidine	1.66 (1.2–2.2)	3.23 (1.9–5.4)
1:3	0.55 (0.31–0.99)	0.89 (0.83–0.97)
1:10	0.68 (0.32–1.4)	1.4 (1.3–1.6)
1:30	1.1 (0.76–1.6)	2.5 (1.9–3.2)
1:100	2.0 (1.1–3.4)	3.1 (2.7–3.6)
Clonidine	0.11 (0.063–0.18)	0.26 (0.15–0.46)

* A significant ($P \leq .05$ difference for the mixture A_{50} from the theoretical additive A_{50}, indicating synergy.

A_{50} and CL of the total mixture is calculated by linear regression of the dose-response curve and resolved into its component parts according to the dosing ratio. This point is plotted on the isobolograph. Thus, for a ratio of 1:3 of clonidine/morphine, the total A_{50} is 0.267 mg/kg (table 1), representing 0.20 mg/kg of morphine (*i.e.*, three-fourths of the total dose) plus 0.067 mg/kg of clonidine (*i.e.*, one-fourth of the total dose). This point is plotted as (0.067,0.2) on the morphine-clonidine isobolograph (fig. 2); likewise, the CL for the total dose are also resolved into the two components. In this example, the clonidine contribution to the A_{50} of the mixture is close to that of clonidine alone (0.11 mg/kg; table 1). The theoretical additive A_{50} for clonidine + morphine is calculated from the A_{50} for morphine such that $A_{50add} = A_{50mor}/(p_1 + Rp_2)$ where R is the potency ratio of morphine to clonidine (16 in this example), p_1 is the proportion of morphine in the total dose and p_2 is that of clonidine. Thus, the theoretical additive A_{50} for this combination is $[1.77/(0.75 + 16 \times 0.25)] = 0.37$ mg/kg. The t test applied to the potency ratio between the A_{50} for the mixture and the A_{50} for the theoretical additive point reveals no significant difference; thus, this combination presents an additive interaction. A graphic illustration on the isobologram (fig. 2) shows that the confidence intervals of these two points do overlap. The A_{50} data for each morphine-clonidine interaction are similarly plotted. The total A_{50} values for each mixture of clonidine to morphine do not differ from their respective additive point; thus, the conclusion is that of at all combinations

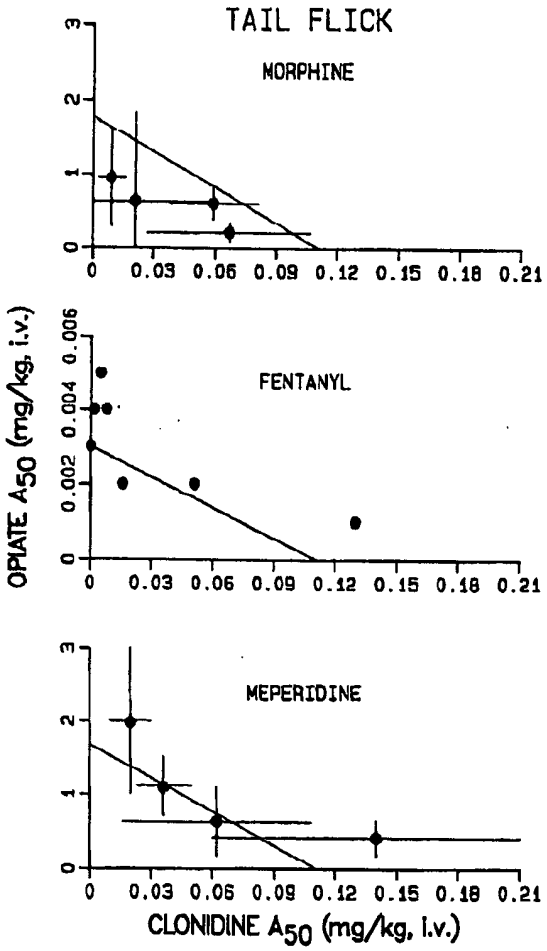

Fig. 2. Isobolograms for the A_{50} for clonidine plotted against morphine, fentanyl and meperidine after i.v. injection in the rat TF test. In each graph the solid line represents the additive line constructed by joining the A_{50} doses for clonidine with the A_{50} dose of the opiate. The CL for the theoretical additive points on the additive line and for the actual mixtures are resolved into the clonidine (horizontal) and opiate (vertical) components and shown on the graphs. The isobol points are determined from the A_{50} doses of ratios of clonidine to morphine or meperidine (from left to right) of 1:100, 1:30, 1:10 and 1:3 and of clonidine to fentanyl of 1:2, 1:1, 1:10, 2:1, 10:1 and 30:1. The CL are omitted for the additive points and in the graph for fentanyl for the sake of clarity.

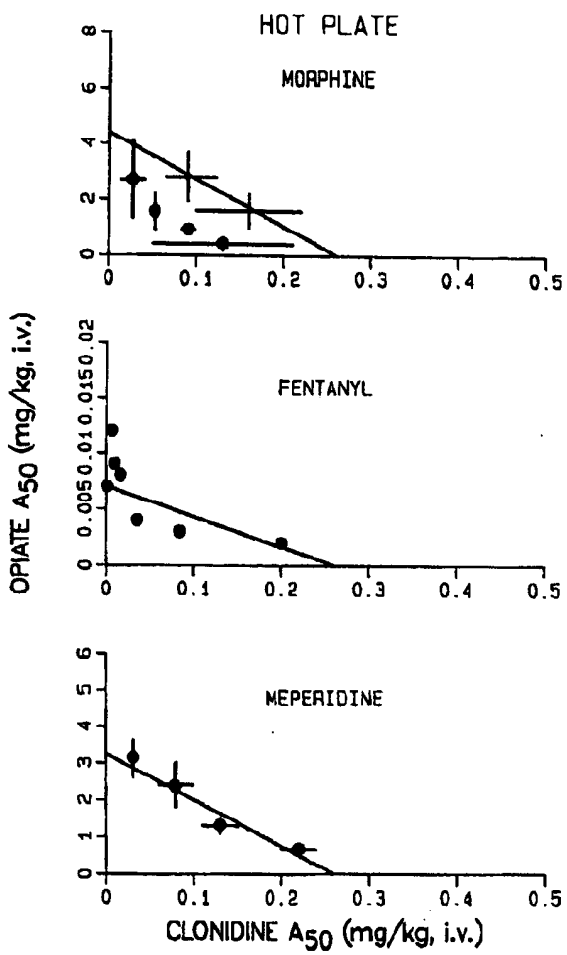

Fig. 3. Isobolograms for the A_{50} for clonidine plotted against morphine, fentanyl and meperidine after i.v. injection in the rat HP test. In each graph the solid line represents the additive line constructed by joining the A_{50} doses for clonidine with the A_{50} dose of the opiate. The CL for the theoretical additive points on the additive line and for the actual mixtures are resolved into the clonidine (horizontal) and opiate (vertical) components and shown on the graphs. The isobol points are determined from the A_{50} doses of ratios of clonidine to morphine or meperidine (from left to right) of 1:100, 1:30, 1:10 and 1:3 and of clonidine to fentanyl of 1:2, 1:1, 1:10, 2:1, 10:1 and 30:1. The CL are omitted on the additive line except where synergy occurs and in the graph for fentanyl for the sake of clarity.

tested in the TF test, morphine and clonidine produce an additive interaction. The nonlinear function of the isobologram with a negative curvature suggests a trend toward a supra-additive interaction between morphine and clonidine in the TF test. A similar pattern is seen in the HP test, with the added condition that the interactions between clonidine and morphine at 1:10 and 1:30 are synergistic (fig. 3). As in the TF test, the negative curvature of these isobolograms further suggest a trend toward supra-additivity. The mixture A_{50} and additive A_{50} points are represented with their respective CL in the isobolograms.

In contrast, we find that for fentanyl in the TF test (fig. 2) and the HP test (fig. 3), there is no negative curvature of the isobols; rather, the points of the isobols appear to be scattered about the additive line. No points are significantly different from their respective theoretical additive points in either the TF or the HP test. It is interesting to see that at ratios ranging from 1:1 of clonidine to fentanyl to 2:1, the isobolographic points are high above the additive line but still within the CL of fentanyl. The data shown in both tests suggest an additive interaction between clonidine and fentanyl after i.v. administration.

Meperidine showed a similar distribution of the data points on the isobolograms in the TF and HP tests. There was considerable negative curvature of the points deviating from the additive line in the TF test, but none of the points are significantly different from their respective additive points (fig. 2). The results seen with the HP test were similar to the TF (fig. 3).

Because the shape of isobolograms may change at different levels of effect, isobols for doses producing 25, 50 (A_{50} dose), 75 and 100 %MPEs are also constructed. Such a graph is shown for morphine in the TF test (fig. 4). It is apparent that the

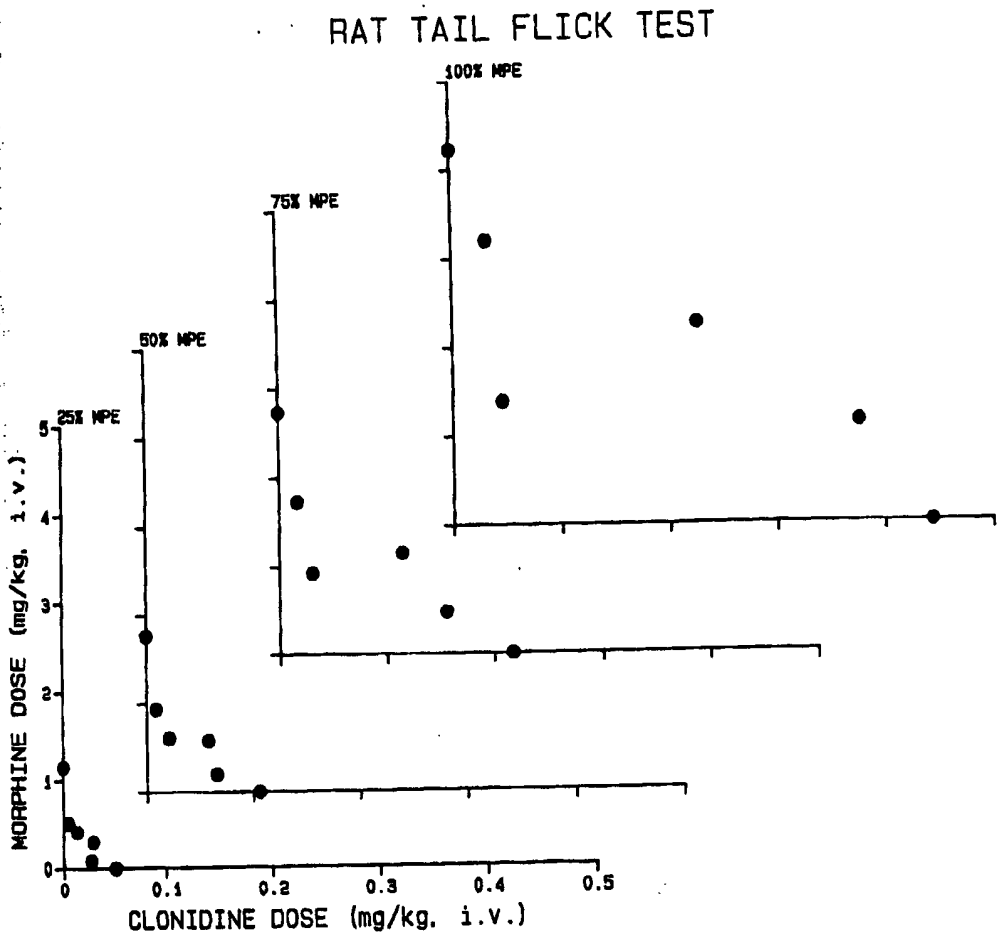

Fig. 4. Isobolographic representation of clonidine *vs.* morphine at 25, 50, 75 and 100 %MPE levels of effect in the rat TF test. The points on the isobols represent, from left to right, clonidine to morphine ratios of 1:100, 1:30, 1:10 and 1:3.

shape of the isobologram is essentially unchanged for each level of effect shown, and the negative curvature of the isobol is present at each level of effect. A similar pattern was seen for morphine in the HP test. Moreover, the isobolographic pattern for the combinations of clonidine and fentanyl and clonidine and meperidine were similar throughout all levels of effect (data not shown) in both the TF and HP tests.

Antinociceptive effects of clonidine or opiates i.t. Clonidine, fentanyl, morphine and meperidine produced dose-dependent antinociception in both the TF (fig. 5) and HP tests after i.t. administration. The curves for the opiates were parallel. The rank-order of potency was fentanyl = morphine > clonidine > meperidine in both of the tests. The A_{50} values in the TF test were 1.4, 1.2, 432 and 44 μg for morphine, fentanyl, meperidine and clonidine, respectively (table 2). In the HP test, the A_{50} values were 0.72, 1.6 and 101 μg for morphine, fentanyl and clonidine, respectively (table 2). The maximal effect seen with meperidine was 44 %MPE at 800 μg; no A_{50} was calculated.

Interaction of clonidine and opiates i.t. Clonidine produced a peak effect at 15 min after injection, fentanyl at 1 min and meperidine and morphine at 5 min after injection. Thus, all testing of the interaction between opiates and clonidine was done at 15 min after injection. The duration of the peak effects of morphine and meperidine extended to overlap with the onset of the peak effect of clonidine. For fentanyl, a second series of experiments was performed in which the timing of injections was staggered so that the peak effect of fentanyl and clonidine coincided. The total A_{50} values for each clonidine-opiate combination are shown in table 2. For each combination, the dose-response curves are parallel to the dose-response curve for morphine and for clonidine within each test.

Isobolographic analysis of i.t. clonidine-opiate interactions. Isobolographs for the interaction of clonidine with morphine, fentanyl or meperidine are constructed as described above. The A_{50} point for the combination of clonidine with morphine is significantly ($P \leq .05$) different from the theoretical additive A_{50}, clearly indicating a supra-additive effect (fig. 6). This strong negative curvature of the isobol is evident at all levels of effect examined (fig. 7); thus it appears that the synergistic effect occurs throughout the dose-response curve. Whereas there is a positive cooperativity between morphine and clonidine in the HP test, it is not interpreted as a synergistic event because the A_{50} point for the morphine-clonidine combination is not significantly ($P > .05$) different from the additive point (fig. 8). Moreover, the shift in the morphine dose-response curve is not significant. However, a strong negative curvature of the isobol was evident at all levels of efficacy examined, suggesting a trend toward supra-additivity.

The isobol for the clonidine-fentanyl when given simultaneously in the TF test also shows a negative curvature, but the A_{50} point for the combination of clonidine and morphine is not different from the additive point for clonidine and fentanyl. In contrast, the A_{50} of the clonidine-fentanyl combination after staggered administration is significantly ($P \leq .05$) less than the predicted additive A_{50}, clearly indicating synergy (fig. 6). This negative curvature of the isobol is found for all magnitudes of responses examined in the TF test (fig. 7). Likewise, in the HP test the interaction between clonidine and fentanyl after i.v.

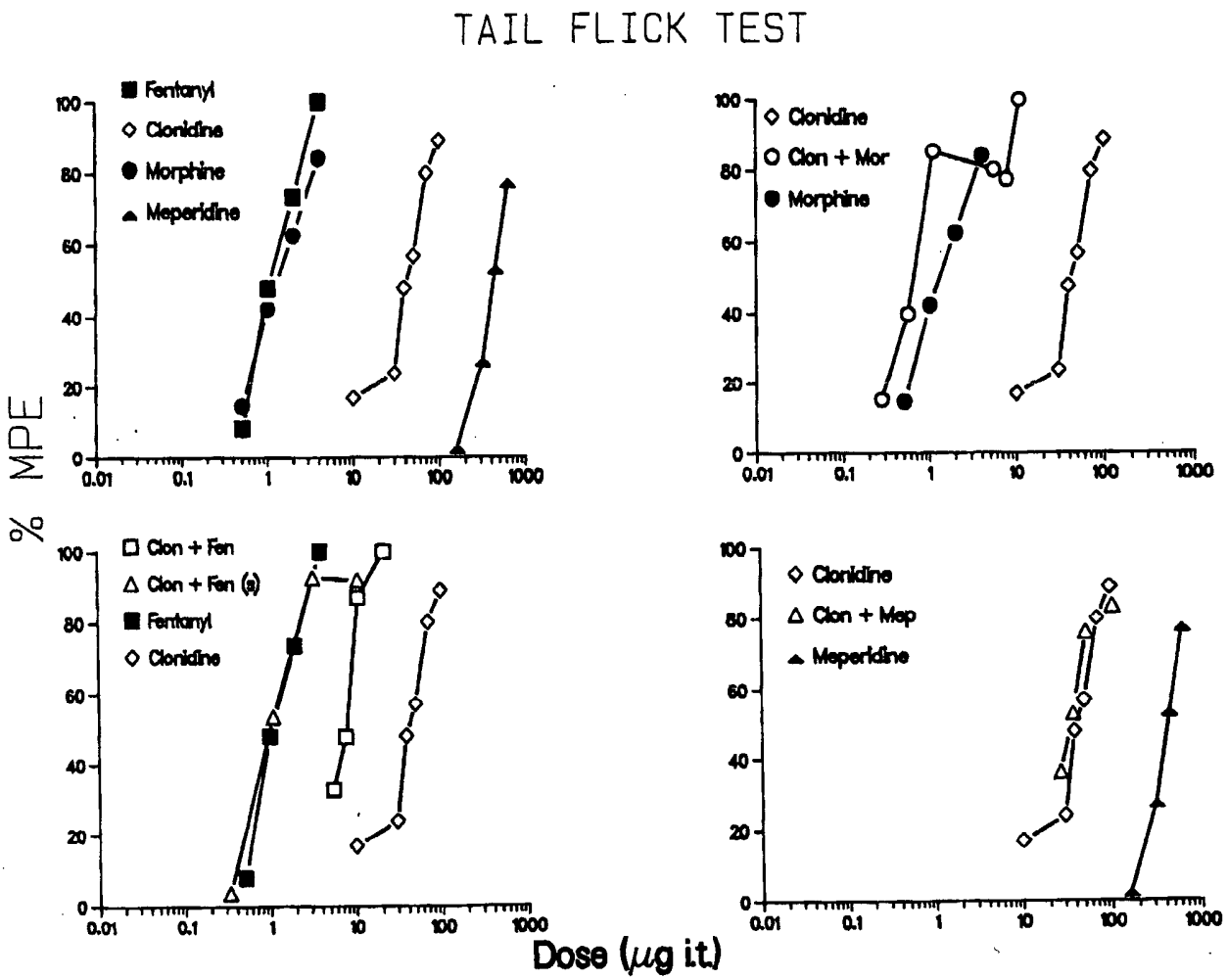

Fig. 5. The dose-response curves in the rat TF test for clonidine (Clon), fentanyl (Fen), morphine (Mor) and meperidine (Mep) administered i.t. are shown in the top left panel. Data were collected at the time of peak effect for each dose. The dose-response curves do not deviate from parallelism. In each panel, the opiate dose-response curve is represented by solid symbols and the corresponding mixture with Clon is represented with the same but open symbols. The dose-response curves for Mor and a fixed ratio of Clon to Mor of 10:1 are shown in the top right panel. The dose-response curves for Fen and a fixed ratio of Clon to Fen of 10:1 given simultaneously and at staggered (s) time intervals are shown in the bottom left panel. The bottom right panel shows the dose-response curves for Mep and a fixed ratio of Clon to Mep of 1:3. Within each panel, statistical tests of parallelism of the dose-response curves failed to show a difference. The doses represented are total (Clon + opiate) doses; $n = 5$ rats/dose in each curve. Except for the simultaneously administered Fen plus Clon, the shifts in the dose-response curves of the opiates were significant ($P \leq .05$) when compared to the opiate alone.

administration is synergistic for the staggered drug injections (fig. 8).

The coadministration of meperidine and clonidine also produces an A_{50} point for the combination that is well below the additive line of the isobologram and significantly different ($P \leq .05$) from the theoretical additive point (fig. 6). As with morphine, this strongly negative curvature of the isobol is present throughout the entire range of effect in the TF test (fig. 7), indicating a synergistic interaction between meperidine and clonidine. Inasmuch as we could not determine an A_{50} dose for meperidine in the HP test after i.t. administration, it is not possible to construct a reliable isobol as with the TF test.

Discussion

Clonidine, morphine, fentanyl and meperidine all produce parallel dose-dependent antinociception in the TF and HP tests after i.v. administration. The dose-response curves for the combinations of clonidine and opiates are parallel after i.v. administration in either test. Thus, opiate and *alpha*-2 adrenergic receptor-mediated mechanisms may produce antinociception by acting through a final common pathway.

Several studies suggest a synergistic interaction between *alpha*-2 and opiate agonists with regard to antinociception. Drasner and Fields (1988) showed that systemic morphine plus i.t. clonidine are synergistic in the rat TF model. Murata *et al.* (1989) reported that systemically administered clonidine and morphine are synergistic because combinations of clonidine and morphine at doses that alone produce little effect inhibit responses of wide dynamic range neurons to thermal nociception in the cat. Ossipov *et al.* (1989) showed that a subactive i.t. dose of clonidine shifted the dose-response curve of i.t. morphine to the left in the rat TF test. Wilcox *et al.* (1987) reported potentiation between i.t. morphine and clonidine in the rat TF model and also in suppressing activity of ascending tract neurons evoked by electrical stimulation of c- and A_δ-fibers. In all these studies, however, either a single dose of each drug was administered and the result was greater than the sum

TABLE 2

Potencies of i.t. combinations of opiates and clonidine

Dose-response curves were constructed for fixed ratios of clonidine and fentanyl, morphine and meperidine in the rat TF and HP tests. The drug ratios are identified as clonidine to opiate. The A_{50} values are calculated from the log dose-response curve by linear regression. The clonidine and opiate components of each combination can be derived from the ratio (as described in the text). Each dose was administered by i.t. injection and the animals were tested at the time of peak effect. $n = 6$ rats per dose.

	A_{50} μg (95% C.L.)	
	TF Test	HP Test
Fentanyl	1.2 (0.91–1.6)	1.6 (0.98–2.57)
Clonidine/fentanyl, 10:1	7.26 (4.40–14.3)	14.3 (10.2–20.6)
Clonidine/fentanyl, 10:1(s)	1.06 (0.64–1.8)*	5.15 (5.07–5.23)*
Morphine	1.4 (1.2–1.6)	0.72 (0.39–1.34)
Clonidine/morphine, 10:1	0.825 (0.209–3.30)*	4.29 (2.20–8.36)
Meperidine	432 (400–467)	800 μg = 46 %MPE
Clonidine/meperidine, 1:3	35 (16–69)*	77.3 (58.3–102)
Clonidine	44 (37–52)	101.1 (81.7–125)

* A significant ($P \leq .05$) difference for the mixture A_{50} from the theoretical additive A_{50}, indicating synergy.

of effects produced by each dose alone, or a fixed dose of one drug caused a significant shift to the left in the dose-response curve of the other drug. Although such studies may indicate a positive interaction between two drugs or treatments, the analysis of the nature of the interaction can be more rigorous. Moreover, when the dose of one component is kept constant whereas that of the other varies to establish a dose-response curve, the ratio between the two components change over the range of the curve. This change in ratio may be important, as Gessner and Cabana (1970) showed that an interaction between two drugs may be either synergistic or additive, depending on the dose ratio. Thus, the isobolographic analysis of dose-response curves of fixed ratios of drugs are presented in this paper as a more rigorous means to examine drug-drug interactions. Our results substantiate the reports that i.t. administered morphine and clonidine act in a synergistic fashion and extend these observations to include meperidine but not fentanyl. The nature of the interaction between opiates and clonidine after i.v. administration may be either additive or supra-additive, depending on the opiate used, ratio of clonidine to opiate and the test used.

The isobolographic means of analysis for drug-drug and site-site interactions has been described by Loewe (1953, 1957) and later by Gessner (1974). Yeung and Rudy (1980) used isobols to determine that the application of morphine spinally and supraspinally is supra-additive; their interpretation was that the points obtained from the analysis of dose-response curves of combination of routes formed a concave isobol with a strongly negative curvature, rather than a linear one described by the line of additivity. Roerig *et al.* (1984, 1988) also utilized isobols to show that i.c.v. and i.t. morphine are synergistic in the mouse, and that this synergy is lost in the presence of tolerance to morphine. Likewise, Roerig and Fujimoto (1988) used isobolographic analysis to evaluate the interaction of morphine and β-endorphin in mice. In their studies, synergy is defined when the points of the isobol and the 95% CL falling well below the line of additivity; overlapping of the confidence intervals with the additive line indicates additivity. Schmidt *et al.* (1986) used a similar approach in examining the interaction

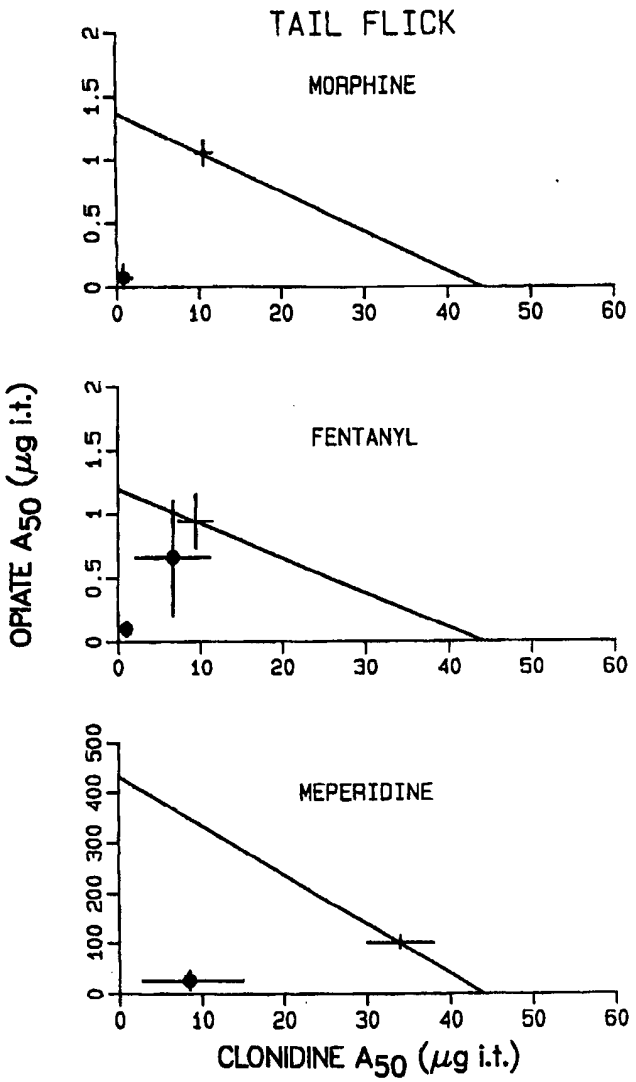

Fig. 6. Isobolograms for the A_{50} for clonidine plotted against morphine, fentanyl and meperidine after i.t. injection in the rat TF test. In each graph the solid line represents the additive line constructed by joining the A_{50} doses for clonidine with the A_{50} dose of the opiate. The CL for the theoretical additive points on the additive line and for the actual mixtures are resolved into the clonidine (horizontal) and opiate (vertical) components and shown on the graphs. These points represent dose ratios of clonidine to morphine or fentanyl of 10:1 and of clonidine to meperidine of 1:3. The A_{50} point closer to the additive line represents simultaneous administration of fentanyl and clonidine and that closer to the origin represents staggered dosing of these drugs.

of nalbuphine with tripelennamine in the mouse writhing test. They determined that the interaction was additive inasmuch as the isobol for the combinations remained within the zone of additivity defined by the upper and lower confidence intervals of the ED_{50} for each drug alone (as described under "Results"). Tallarida *et al.* (1989) described recently a statistical approach to the isobolographic interpretation of drug-drug interactions. The methodology described involves determining the ED_{50} of each drug alone along with the 95% confidence intervals from regression analysis of the dose-response curves. The CL are distributed equally about the ED_{50}. From the ED_{50} values and their associated variances, the dose ratio of drug 1 and 2, and the potency ratio, a theoretical ED_{50} and its CL are calculated for a given ratio of two drugs. This value is compared to the ED_{50} actually obtained with the mixture of the drugs at the

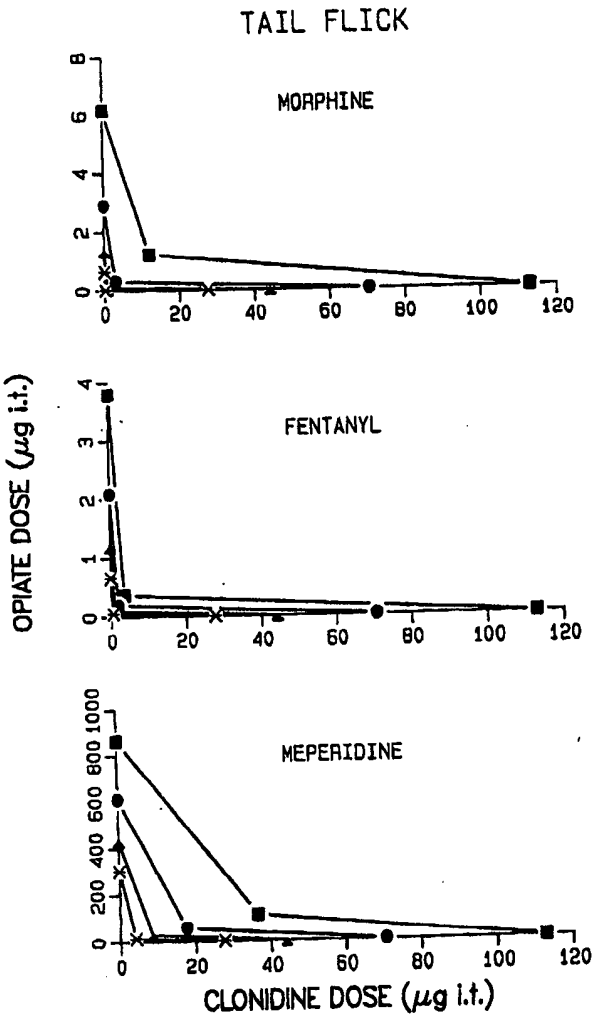

Fig. 7. Isobolographic representation of the combination of clonidine to morphine of 10:1, clonidine to fentanyl of 10:1 (staggered dosing) and clonidine to meperidine of 1:3 administered i.t. in the rat TF test. The doses calculated to produce the 25 (*), 50 (▲), 75 (●) and 100 (■) %MPE are shown in ascending order on each graph.

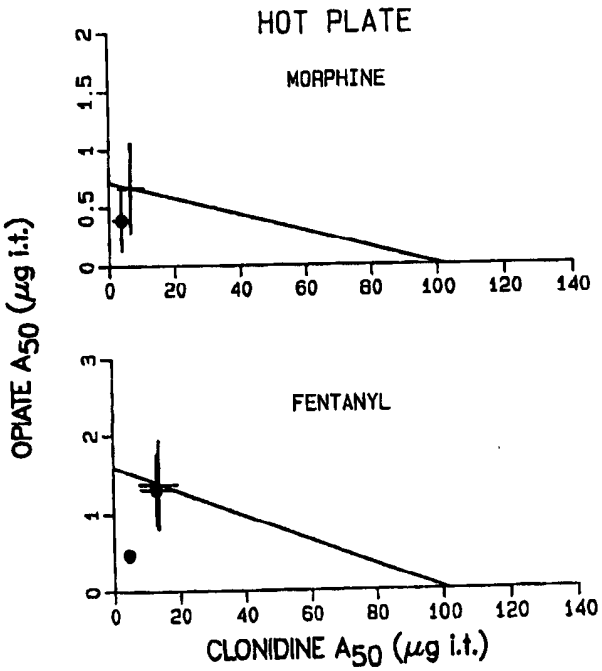

Fig. 8. Isobolograms for the A_{50} for clonidine plotted against morphine, fentanyl and meperidine after i.t. injection in the rat HP test. In each graph the solid line represents the additive line constructed by joining the A_{50} doses for clonidine with the A_{50} dose of the opiate. The CL for each the theoretical additive points on the additive line and for the actual mixtures are resolved into the clonidine (horizontal) and opiate (vertical) components and shown on the graphs. These points represent dose ratios of clonidine to morphine or fentanyl of 10:1 and of clonidine to meperidine of 1:3. The A_{50} point closer to the additive line represents simultaneous administration of fentanyl and clonidine and that closer to the origin represents staggered dosing of these drugs.

same dose ratio by applying a *t* test to the potency ratio; a significant difference indicates synergy. This method is valid whether the dose-response curves are parallel or not; and represents an alternative to the suprapictorial analyses of isobolograms reported by others (Roerig *et al.*, 1984; Roerig and Fujimoto, 1988). A detailed derivation of the methods used and their application are presented by Tallarida *et al.* (1989).

Fentanyl showed some variation in its effects in that the points on the isobols for dosage ratios high in fentanyl are above the additive line but well within the CL of fentanyl itself, probably reflecting normal variations in the measurements of the A_{50} values rather than suggesting a subadditive interaction. A subadditive interaction is also ruled out because the A_{50} points of the isobol were not different from the theoretical additive points. The negative curvature of the morphine-clonidine isobols in the TF and HP tests with synergistic points identified in the HP test indicate a strong positive interaction between morphine and clonidine after i.v. administration. The interaction between clonidine and meperidine is clearly additive after i.v. administration.

The effects seen after i.t. administration of the drugs is much more robust than those seen after i.v. administration, and the isobols produced by each i.t. administered opiate-clonidine combination show a strong negative curvature. These results show a clear indication of supra-additivity between the spinal opiate and *alpha*-2 adrenergic sites with regard to antinociception. The most robust interactions observed were at the spinal reflexive TF test after i.t. administration, leading us to conclude that the most likely site of interaction between opiates and *alpha*-2 adrenergic agonists is spinal. The spinal site of interaction has been suggested by others, because clonidine, unlike morphine, retains its potency after spinal transection (Hylden and Wilcox, 1983; Howe *et al.*, 1983; Spaulding *et al.*, 1979; Wilcox *et al.*, 1987) and does not produce antinociception supraspinally (Ossipov and Gebhart, 1983). The observation that the simultaneously administered i.t. combination of fentanyl and clonidine was additive whereas the staggered injections of the same drug combination was synergistic underscore the importance of establishing the onset of peak effect of drug activity and accounting for duration of action. Clearly, pharmacokinetic factors could influence the outcome of drug interaction studies, and important data could be lost if these factors are not considered.

The absence of definitive synergism after i.v. administration could be attributed primarily to two possibilities. First, if the site of interaction is indeed spinal, then systemic administration of the drugs may dilute the overall efficacy of clonidine, because the portion of clonidine reaching supraspinal sites might act to inhibit antinociception (Ossipov and Gebhart,

1983). Secondly, systemically administered morphine acts spinally and supraspinally, and activates descending inhibitory projections, many of which are noradrenergic and can act on spinal *alpha*-2 adrenoceptors (Wigdor and Wilcox, 1987; Yaksh, 1985). Consequently, the sites at which clonidine would act spinally are already being activated indirectly by the opiate. Thus, this antinociceptive system may already be maximally effective and the further addition of clonidine would fail to produce any additional effect other than additive.

Our data, coupled with the reports cited above, strongly implicate a spinal site of interaction between opiate and *alpha*-2 adrenergic receptors in producing antinociception. Activation of either class of receptors produces antinociception in whole animal models (Hylden and Wilcox, 1983; Yaksh, 1985, Solomon and Gebhart, 1989, Ossipov *et al.*, 1989) and inhibits spinal nociceptive responses in electrophysiologic studies (Murata *et al.*, 1989; Wilcox *et al.*, 1987). Opiates and *alpha*-2 receptors share a common mechanism: both activate a G-protein coupled receptor which enhances a K^+ current; enhancement of this current leads to hyperpolarization of neurons which may inhibit neuronal firing and/or decrease neurotransmitter release (Miyake *et al.*, 1989). If *alpha*-2 adrenergic and opiate receptors reside on the same neuron, it is possible that a cooperativity exists between the two types of receptors. Alternatively, it is not unreasonable to suggest that activation of the *alpha*-2 adrenergic and opiate receptors may elicit an enhanced effect by independently altering intracellular mechanisms coupled to G-protein activation.

The interaction between opiates and clonidine is one of positive interaction, and may be described as synergistic under certain conditions. It appears that morphine provides the most robust positive interaction and fentanyl the least, and that the degree of cooperativity is most robust after i.t. administration. These conclusions are consistent with the view that *alpha*-2 adrenoceptor-mediated antinociception occurs at the spinal level. Moreover, these data add to our understanding of nociceptive processing and may have important clinical implications. Whereas earlier studies established that *alpha*-2 adrenergic antagonists could attenuate opiate receptor-mediated antinociception and that the converse also occurred, the effects of receptor antagonists on the types of drug interactions described herein have not been reported and deserve further investigation.

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tolerant of aspirin also may suffer a severe reaction after administration of one of these drugs. Some of the propionic acid derivatives have prominent inhibitory effects on leukocyte function; naproxen is particularly potent in this regard. While the compounds do vary in potency, this is not of obvious clinical significance. All are effective antiinflammatory agents in various experimental animal models of inflammation; all have useful antiinflammatory, analgesic, and antipyretic activities in human beings. Although all of these compounds can cause gastrointestinal side effects in patients, these are usually less severe than with aspirin.

It is difficult to find data on which to base a rational choice among the members of the propionic acid derivatives, if in fact one can be made. However, in relatively small clinical studies that compared the activity of several members of this group, patients preferred naproxen in terms of analgesia and relief of morning stiffness (*see* Huskisson, *in* Symposium, 1983a; Hart and Huskisson, 1984). With regard to side effects, naproxen was the best tolerated, followed by ibuprofen and fenoprofen. There was considerable interpatient variation in the preference for a single drug and also between the designations of the best and the worst drug. Unfortunately, it is probably impossible to predict *a priori* which drug will be most suitable for any given individual. Nevertheless, more than 50% of patients with rheumatoid arthritis probably will achieve adequate symptomatic relief from the use of one or another of the propionic acid derivatives, and many clinicians favor their use instead of aspirin in such patients.

Drug Interactions. The potential adverse drug interactions of particular concern with propionic acid derivatives result from their high degree of binding to albumin in plasma. However, the propionic acid derivatives do not alter the effects of the oral hypoglycemic drugs or warfarin. Nevertheless, the physician should be prepared to adjust the dosage of warfarin because these drugs impair platelet function and may cause gastrointestinal lesions.

Ibuprofen

Ibuprofen is supplied as tablets containing 200 to 800 mg; only the 200-mg tablets (ADVIL, NUPRIN, others) are available without a prescription.

For rheumatoid arthritis and osteoarthritis, daily doses of up to 3200 mg in divided portions may be given, although the usual total dose is 1200 to 1800 mg. It also may be possible to reduce the dosage for maintenance purposes. For mild-to-moderate pain, especially that of primary dysmenorrhea, the usual dosage is 400 mg every 4 to 6 hours as needed. The drug may be given with milk or food to minimize gastrointestinal side effects. The safety and efficacy of ibuprofen in children have not been established. Ibuprofen has been discussed in detail by Kantor (1979) and by Adams and Buckler (in Symposium, 1983a).

Pharmacokinetics and Metabolism. Ibuprofen is rapidly absorbed after oral administration, and peak concentrations in plasma are observed after 1 to 2 hours. The half-life in plasma is about 2 hours. Absorption also is efficient, although slower, from suppositories.

Ibuprofen is extensively (99%) bound to plasma proteins, but the drug occupies only a fraction of the total drug-binding sites at usual concentrations. Ibuprofen passes slowly into the synovial spaces and may remain there in higher concentration as the concentrations in plasma decline. In experimental animals, ibuprofen and its metabolites pass easily across the placenta.

The excretion of ibuprofen is rapid and complete. More than 90% of an ingested dose is excreted in the urine as metabolites or their conjugates. The major metabolites are a hydroxylated and a carboxylated compound.

Toxic Effects. Ibuprofen has been used in patients with a history of gastrointestinal intolerance to other NSAIDs. Nevertheless, therapy usually must be discontinued in 10% to 15% of patients because of intolerance to the drug.

Gastrointestinal side effects are experienced by 5% to 15% of patients taking ibuprofen; epigastric pain, nausea, heartburn, and sensations of "fullness" in the gastrointestinal tract are the usual difficulties. However, the incidence of these side effects is less with ibuprofen than with aspirin or indomethacin. Occult blood loss is uncommon.

Other side effects of ibuprofen have been reported less frequently. They include thrombocytopenia, skin rashes, headache, dizziness and blurred vision, and, in a few cases, toxic amblyopia, fluid retention, and edema. Patients who develop ocular disturbances should discontinue the use of ibuprofen.

Ibuprofen is not recommended for use by pregnant women, or by those who are breast-feeding their infants.

Naproxen

The pharmacological properties and therapeutic uses of naproxen have been reviewed by Segre (in Symposium, 1983a), Allison and colleagues (*in* Rainsford, 1985b), and Todd and Clissold (1990).

Pharmacokinetics and Metabolism. Naproxen is fully absorbed when administered orally. The rapidity, but not the extent, of absorption is influenced by the presence of food in the stomach. Peak concentrations in plasma occur within 2 to 4 hours and are somewhat more rapid after the administration of naproxen sodium. Absorption may be accelerated by the concurrent administration of sodium bicarbonate or reduced by magnesium oxide or aluminum hydroxide. Naproxen also is absorbed rectally, but peak concentrations in plasma are achieved more slowly. The half-life of naproxen in plasma is about 14 hours; this value is increased about twofold in elderly subjects and may necessitate adjustment of dosage.

Metabolites of naproxen are almost entirely excreted in the urine. About 30% of the drug undergoes 6-demethylation, and most of this metabolite, as well as naproxen itself, is excreted as the glucuronide or other conjugates.

Naproxen is almost completely (99%) bound to plasma proteins following normal therapeutic doses. Naproxen crosses the placenta and appears in the milk of lactating women at approximately 1% of the maternal plasma concentration.